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TRANSMITTAL FORM

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Total Number of Pages in This Submission

Application Number	08/838,486
Filing Date	April 7, 1997
First Named Inventor	Steinunn Baekkeskov
Art Unit	1644
Examiner Name	Gerald R. Ewoldt
Attorney Docket Number	2307AA-031220US

ENCLOSURES *(Check all that apply)*

- [X] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [X] Petition of Denial of Entry of Exhibits and Declaration under 37 CFR 1.195 (6 pgs)
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to TC **Appellants' Brief (Second Revision) Under 37 CFR 41.37 (21 pgs)**
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) (please identify below):

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Firm Name	Townsend and Townsend and Crew LLP		
Signature	J. Liebeschuetz		
Printed name	Joe Liebeschuetz		
Date	July 3, 2006	Reg. No.	37,505

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FEE TRANSMITTAL
For FY 2006

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 215

Complete if Known	
Application Number	08/838,486
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1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-20 or HP = _____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-3 or HP = _____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number) x	_____	= _____

4. OTHER FEE(S)

		Fees Paid ($)
Non-English Specification,	$130 fee (no small entity discount)	
Other (e.g., late filing surcharge):	1) Petition of Denial of Entry of Exhibits and Declaration under 37 CFR 1.195	
	2) Filing of Second Revision of Appellant's Brief (less previously filed fee for Appeal Brief) ($250-$165)	130 85

SUBMITTED BY

Signature	[signature]	Registration No. (Attorney/Agent) 37,505	Telephone 650-326-2400
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60814001 v1

PATENT
Docket No.: 2307AA-031220US
Client Ref. No.: 90-160-5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

Steinunn Baekkeskov et al.

Application No.: 08/838,486

Filed: April 7, 1997

For: IMPROVED METHODS FOR THE DIAGNOSIS AND TREATMENT OF DIABETES

Examiner: Gerald R. Ewoldt

Art Unit: 1644

APPELLANTS' BRIEF (SECOND REVISON) UNDER 37 CFR § 41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the final office action of July 29, 2003 and further to the notice of appeal filed December 29, 2003, appellants submit the following brief.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The Regents of the University of California and Yale University, jointly.

II. RELATED APPEALS AND INTERFERENCES

USSN 08/452,053 ('053 application), the parent of the present case contains claims to methods of diagnosing insulin dependent diabetes mellitus (IDDM) using glutamic acid decarboxylase (GAD). Applicants have requested an interference between the '053 application and US 5,645,998 ('998 patent) assigned to the University of Florida, which has substantially corresponding claims. The '053 application has been allowed and prosecution suspended pending declaration of the requested interference. The present case, which is directed to methods of treatment and pharmaceutical compositions substantially corresponds at least in part to claims to two other patents assigned to the University of Florida, US 6,001,360 ('360 patent), and US 5,762,937 ('937 patent). The '360 and '937 patents are in the same priority lineage as the Florida '998 patent. The disclosure of these patents is substantially similar to that of the present case, and as noted in the request for interference filed May 5, 2003, the earliest conceivable effective filing date of the '360 and '937 patents and that of the present application are only three weeks apart. The '937 Florida patent is cited by the Examiner as anticipating many of the claims present in the present case. An exemplary claim from the '360 Florida patent appears below.

> 1. A method for preventing or delaying the development of clinical symptoms of insulin dependent diabetes wherein said method comprises administering to an animal an essentially pure GAD protein or a fragment thereof which, when administered to an animal, prevents or delays the development of clinical symptoms of insulin dependent diabetes.

Applicants have requested that an interference be declared between the present application and US 6,001,360, and US 5,762,937 under 37 CFR 1.607 and 1.608 (see paper no. filed May 5, 2003). The Examiner has declined to consider this request pending resolution of the issues posed by this appeal. The priority issues for the diagnostic claims in the parent and therapeutic claims and therapeutic claims in the present case involve the same underlying facts vis a vis the University of Florida patents. Therefore, in the interest of judicial economy, it is requested that the relative priority between the present case and the Florida '360 and '937 patents

and the relative priority between the '053 parent of the present case, and Florida '998 be resolved as first and second counts of the same interference.

III. STATUS OF CLAIMS

Claims 31, 35, 50-57, 59 and 62-67 are pending and rejected. Claims 1-30, 32-34, 36-49, 58, and 60-61 are cancelled. All rejected claims are appealed.

IV. STATUS OF AMENDMENTS

An amendment after final was filed canceling claims 49 and 58 and has been entered. All previous amendments have been entered.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention is premised in large part on the discovery that glutamic acid decarboxylase (GAD) is a component of a pancreatic beta cell 64 kDa antigen that is a major autoantigen in insulin dependent diabetes mellitus (IDDM) (also known as type 1 diabetes) (specification at p. 8, lines 32-37). Whereas the pancreatic beta cell 64 kDa antigen is present in pancreatic islets in only minute amounts (specification at p. 3, lines 25-3)), GAD is present in large amounts in the CNS (p. 8, line 36). The discovery of the relationship between GAD and the pancreatic 64 kDa and consequent availability of large amounts of autoantigenic protein gave rise to diagnostic and therapeutic methods of detecting and treating IDDM using GAD (see specification at p. 9, lines 9-14). The diagnostic methods are claimed in the '053 parent application. The therapeutic methods and pharmaceutical compositions are claimed in the present case.

Specifically, independent claim 31 is directed to a method for inhibiting the development of insulin dependent diabetes mellitus by administering to a patient a therapeutically effective dosage of GAD (specification at pp.19-22). Administration of GAD to a patient induces tolerance to the 64 kDa pancreatic autoantigen, thereby inhibiting further destruction of beta pancreatic cells and the clinical symptoms of IDDM that eventually result from this destruction.

Independent claim 62 recites a similar method of treatment except that the wording and format of claim 62 was specifically chosen to follow that of claim 1 from the Florida '360 patent as closely as possible for purposes of interference.

Independent claim 35 recites a composition comprising GAD, which is at least 99% w/w pure, in a pharmaceutically acceptable carrier for parenteral administration to a human patient (specification at pp. 19-22 and p14, line 13).

Dependent claims 54 and 59 specify that the GAD used is lower molecular weight GAD. GAD exists in two forms known as lower and high molecular weight forms, now known as GAD65 and GAD67 respectively (see e.g., specification at p. 37, lines 17-23).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 31, 50-53, 62-67 lack enablement under 35 USC 112, first paragraph.

2. Whether claims 31, 64 and 65 are anticipated by US 5,762,937 under 35 USC 102(e).

3. Whether claims 35, and 54-57 are anticipated by US 5,762,937 under 35 USC 102(e).

4. Whether claims 50-53, 59, 66 and 67 would have been obvious under 35 USC 103(a) over US 5,762,937.

5. Whether claims 35 and 54-57 would have been obvious under 35 USC 103(a) over US 4,086,142 in view of US 4,736,020.

VII. ARGUMENT

1. Claims 31, 50-53, 62-67 are enabled under 35 USC 112, first paragraph

a. Summary of Claimed Methods and Evidence Supporting their Enablement

The therapeutic method of the present claims is a simple one involving a single step of administering a therapeutically effective dosage of GAD to a patient. Several references published subsequent to the invention show that administration of GAD to an animal model of IDDM, a NOD mouse, is effective to inhibit IDDM (see Baekkeskov declaration filed July 22, 2003 at paragraph (5) citing Tisch *et al.*, *Nature* 366, 71-75 (1993); Kaufman, *Nature* 366, 69-71 (1993), Tian *et al.*, *Nature Medicine* 12, 1348 (1996), Peterson *et al.*, *Diabetes* 44, 1478 (1994), and Harrison, *Molecular Medicine* 1, 722-727 (1994)). A phase-I clinical trials has demonstrated

that GAD can safely be administered to humans (see Press Release attached to response of January 5, 2001). A phase-II clinical trial has confirmed safety and shown statistically significant evidence of efficacy in a patients with Late Autoimmune Disease in Adults (LADA), a subset of diabetes masquerading as type II on account of its late onset but which is now regarded as a form of Type 1 diabetes (see Baekkeskov declaration at paragraph (6) and Press Release attached to supplemental communication of July 22, 2003).

(b) Summary of Examiner's Rationale

The Examiner acknowledges that the claimed methods are enabled with respect to their use in a NOD mouse (final office action of July 29, 2003, at p. 2). However, the Examiner denies that the methods are enabled for a patient, notwithstanding the above evidence, on several grounds. First, the Examiner says that although the NOD mouse model may be the best available model, results obtained from it are not predictive of efficacy in humans (final office action at p. 4). Second, the Examiner alleges that the results of a successful phase I safety study is insufficient to support the enablement of the present claims (office action of November 4, 2002 at p. 4). Third, the Examiner discounts the results from a successful phase II trial on the basis that these results were obtained on a related pathology of non-autoimmune origin (final office action at p. 4). Fourth, the Examiner takes the view that the general field of tolerance-inducing therapies was unpredictable at the effective filing date of the application based in part on lack of a successful therapy in the 13 years post filing (office action at p. 4, 3rd paragraph) and the teaching of the specification that care should be taken that administration of compositions does not potentiate the autoimmune response (p. 20, lines 16-19). Fifth, the Examiner cites two articles (Goodnow and Marketletter) as evidence that methods of inducing tolerance that worked in animal models have not proved successful in human in two diseases other than IDDM (final office action at p. 3, last paragraph). Finally, the Examiner raises additional issues with respect to the recitation of "preventing" and "fragment" in claim 62 (office action of February 4, 2003 at pp. 4-5).

(c) The legal standard

The leading case regarding the sufficiency of animal trial to support enablement of treatment in humans under 35 USC 112, first paragraph is *In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995). The *Brana* court reversed a rejection under 35 USC § 112, first paragraph

based on the PTO's refusal to accept data from testing compounds in an animal model of cancer (*id.* at 1444). The animal model at issue in *Brana* was formed by injecting cancer cells into mice. The PTO took the position that the model was not fully representative of human cancers because the mice did not naturally develop cancers (*id.* at 1440). The PTO argued that "in vivo tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, [meaning] in vivo testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans" (*id.* at 1142). The Federal Circuit reversed the rejection as "arbitrary and capricious." The Federal Circuit held that "Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings" (*id.* at 1442).

(d) Analysis

Here, it is not disputed by the Examiner that the presently claimed methods are enabled for an animal model of IDDM, namely, the NOD mouse. The remaining issue is whether the NOD mouse is reasonably predictive of similar results in treating IDDM in other patients, including humans. There is abundant evidence that such is the case. As explained in the declaration of Dr. Baekkeskov submitted July 21, 2003 (Baekkeskov declaration), the NOD mouse is a good model of IDDM in human because both humans and mice develop the same pathological characteristics of autoantibodies and T-cells to GAD (Baekkeskov declaration at paragraph 6). Moreover, positive results in the NOD mouse have been used as evidence to support human clinical trials of a number of drugs to treat IDDM, including humanized OKT3, alpha interferon, and most importantly GAD (see Baekkeskov declaration at paragraph 6). In the case of GAD, both phase I and phase II clinical trials have been conducted. The phase I trial has provided evidence of safety, and the phase II trial has provided statistically significant evidence of efficacy. In the aggregate, the above evidence abundantly supports the conclusion that results in the NOD mouse are reasonably predictive of similar success in humans. Even the Examiner acknowledges, the NOD mouse may be the "best available model" (final office action at p. 4).

The Examiner criticizes reliance on the phase I trial of GAD on the basis that a phase I trial cannot show freedom from long-term side effects or establish efficacy (office action of November 4, 2002 at p. 4). Appellants acknowledge that a phase I trial cannot preclude the possibility of long term side effects, nor establish efficacy. Nevertheless, the fact that a phase I

trial has been allowed to occur is an indication that a disinterested body of experts (i.e., the FDA or equivalent in other countries) has concluded from the relevant preclinical data including animal models, such as those in the references cited in the Baekkeskov declaration at paragraph (5)), that the trial has a reasonable chance of success. This unsolicited and disinterested opinion of experts in the field stands in opposition to the office action's own assessment of the animal models. The Examiner dismisses these comments regarding the opinion of a disinterested body of experts as mere attorney argument (office action of February 4, 2003 at p. 3). However, in fact appellants' comments regarding the significance of a phase I trial mirror those in the MPEP:

> Before a drug can enter human clinical trials, the sponsor, often the applicant must provide a convincing rationale to those <u>especially</u> skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary.
>
> MPEP 21707.03.

In view of the corroboration provided by the MPEP, a declaration should not be required for acceptance of appellants' position that the fact that a phase I trial has been allowed to occur is an indication that a body of experts has concluded from the relevant preclinical data including animal models that treatment in humans has a reasonable chance of success

The Examiner discounts the successful phase II trial employing GAD on the basis that it was conducted on a related pathology of non-autoimmune origin (final office action at p. 4). The notion that anyone would conduct a phase II clinical trial of GAD on patients not suffering from autoimmune attack of GAD to whom the treatment would be of no apparent benefit is implausible, and in fact mistaken. The phase II trial was conducted on a subclass of diabetes patients termed LADA. LADA is an acryonym for Late *Autoimmune* Disease in Adults, a term that unmistakably refers to an autoimmune disease. As was stated in the materials describing the phase II trial and the Baekkeskov declaration, the patients of this subclass of patients are suffering from autoimmune attack and do have autoantibodies to GAD, as in type I patients.

Next the Examiner points to general unpredictability in the field of inducing immunotolerance based in part in part on lack of a successful therapy in the 13 years post filing (final office action at p. 4, 3rd paragraph) and the teaching of the specification that care should be taken that administration of compositions does not potentiate the autoimmune response (p. 20, lines 16-19). Appellants initially note that the issue at hand is the enablement of claims containing a single step of administering a therapeutically effective amount of GAD to a patient. Practice of such a method is not dependent on an understanding of the entire field of immunotolerance. Second, a period of 13 years or more between the appearance of a drug in the laboratory and its final approval for use by the FDA or similar body is not unusual. Patent applications are by necessity filed at an early date in this process before public disclosure. Third, although the Examiner is correct that the present specification does indicate that care should be taken not to potentiate an immune response, general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art at the date of the invention (see Baekkeskov declaration at paragraph (4)). For example, a standard immunology textbook available at he priority date of the invention indicates that either low or high dosages of antigen favor a tolerogenic response, whereas intermediate dosages favor an immunogenic response (Benjamini & Leskowitz, *Immunology: A Short Course* (Liss, 1988) at p. 256).

The Examiner's criticism that the materials describing the phase II clinical trial do not describe the dosage as being "high" or "low" (final office action at p. 4) is oversimplistic. A dosage is not described as "high" or "low" in isolation. Rather, guidance that the desired tolerogenic effect can be achieved at high or low dosage represents a principle that if the desired effect is not achieved by the initially chosen dosage, it can likely be achieved by varying the dosage. Performing clinical trials at varying dosage is standard practice in the art. As the Examiner has acknowledged "[i]t would have been prima facie obvious to one of ordinary skill at the time the invention was made to optimize the dosage of the GAD administered in the method of the reference [US 5,762,947], said optimization falling well within the purview of one of skill in the art at the time of the invention" (office action of November 4, 2000 at p. 7).

Next , the Examiner cites Goodnow and a Marketletter article, as evidence that methods of inducing tolerance that worked in animal models were a complete failures in treatment of humans with multiple sclerosis and rheumatoid arthritis (final office action at p. 3,

last paragraph). Results reported for other diseases are less significant and do nothing to change the undisputed evidence that is directly applicable to insulin dependent diabetes. That is, treatment of GAD has been showed to induce tolerance in numerous independent studies on a NOD mouse model, and successful phase I and II human clinical trials have been completed. Also, it is noted that the Examiner omits to mention parts of the articles that do not support his positions. For example, the Marketletter article reports that "substantial improvements" above baseline were observed in the Collerol trial and that Autoimmune still "firmly believes in its technology."

The Examiner's allegation of inconsistency between remarks in paragraph (4) of the first Baekkeskov declaration regarding animal models and appellants' above position regarding the alleged failures in clinical trials of multiple sclerosis and rheumatoid arthritis is incorrect and an obfuscation of the real issues. It is undisputed that the presently claimed methods are enabled in an animal model. It is common sense that alleged failures in clinical trials of multiple sclerosis and rheumatoid arthritis using agents unrelated to GAD are less relevant to the claimed methods than the successful clinical trials using GAD in a subset of patients undergoing autoimmune attack of GAD.

Finally, the Examiner comments on two issues specifically applicable to claim 62, namely the recitation of "preventing" and "fragment" of GAD. Initially, it is noted that claim 62 substantially corresponds to claim 1 of US 6,001,360 from which it was copied for purposes of provoking an interference. Claim 1 of '360 also contains the offending terms "preventing" and "fragment." Thus, the USPTO has allowed a substantially similar claim to others.

The Examiner objects to the term "preventing" on the basis that it implies "absolute prevention" which in the Examiner's view cannot be achieved (office action of November 4, 2002, sentence bridging pp. 4-5). In response, it is submitted that in the context of preventive medicine the term "preventing" is used more generally than to imply absolute prevention. Few if any preventive measures achieve absolute prevention in every patient. In any event, it is not implausible that treatment of GAD can prevent onset of clinical symptoms of IDDM at least in some patients. Clinical symptoms of IDDM do not start until the majority of β-pancreatic islet cells have been destroyed. Onset of clinical disease is preceded by a long prodromal period in which progressive destruction of β-pancreatic cells occurs and

autoantibodies to GAD are present (see specification at paragraph bridging pp. 1-2 and also Tian, *Nature Medicine* 12, 1348 (1996), of record, at p. 1348). If autoantibodies are detected early in the prodromal period (using the diagnostic methods disclosed in the application) and GAD is then administered, it will not restore any pancreatic destruction that has already occurred, but will stop or inhibit further destruction. If administration of GAD is successful in preventing further destruction, and the patient does not reach the point at which sufficient β-pancreatic cells have been destroyed for clinical symptoms then diabetes has been prevented.

With respect to fragments, the Examiner alleges that claim 62 encompasses administration of fragments having only a single amino acid, which the Examiner says would be highly unpredictable (Office action of February 4, 2003 at p. 5, first paragraph). In response, it is not reasonable to construe the claims as encompassing administering "fragments" consisting of only a single amino acid. Claim 62 specifies a fragment which "when administered to the patient, prevents or inhibits the development of insulin dependent diabetes." The recital of a specific function for a fragment implies that the fragment has sufficient structure to provide that function. Therefore, claim 62 does not encompass single amino acids or other short fragments too small to achieve the desired function of preventing or inhibiting development of insulin dependent diabetes.

In conclusion, the Examiner has not met his burden of proving that successful results obtained in a mouse model (which the Examiner acknowledges is enabled by the specification) are not predictive of similar results in other patients, including humans, particularly given the evidence from clinical trials of GAD at discussed above. At most, the Examiner argues that the NOD mouse is not a perfect model of IDDM in humans. That the NOD mouse does not mimic the human disease in every respect was also true of the mouse model in *Brana* and probably every other mouse model of human disease. As *Brana* made clear, rejection of data from a mouse model for this reason is arbitrary and capricious.

2. Alleged Anticipation of Claims 31, 64 and 65 by US 5,762,937 under 35 USC 102(e) should be Determined by Interference

For purposes of this appeal, appellants do not dispute the merits of the rejection. However, appellants do allege that they invented the above claims before the inventors of the

'937 patent. Because the rejection is made at least in part over the claims of the '937 patent (final office action at paragraph 7), this issue can be resolved only by interference. Appellants have formally requested an interference with the '937 patent, as noted above.

3. Alleged Anticipation of Claims 35 and 55-57 under 35 USC 102(e) should be Determined by Interference; Claim 54 is not Anticipated by US 5,762,937

For purposes of this appeal, appellants do not dispute the merits of the rejection with respect to claims 35 and 55-57. However, appellants do allege that they invented the above claims before the inventors of the '937 patent. Because the rejection is made at least in part over the claims of the '937 patent (final office action at paragraph 7), this issue can be resolved only by interference. Appellants have formally requested as interference with the '937 patent, as noted above.

Appellants deny that claim 54 is anticipated by the '937 patent. The Examiner's rationale is summarized in the office action of February 4, 2003 at paragraph 15. The Examiner relies particularly on Example 14 of the '937 patent as teaching a composition comprising GAD. The Examiner says that lower molecular weight GAD is the only molecular weight GAD taught by the reference and that lower molecular weight GAD would thus inherently be present. In the final rejection, the Examiner adds that the specification refers repeatedly to the lower molecular weight antigen (the 64 kDa antigen) (final office action at paragraph 9).

In response, it is submitted that the '937 patent does not teach either expressly or under principles of inherency a composition comprising lower molecular weight GAD in at least 99% purity, as specified by claim 54 (including the elements from antecedent claim 35). Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention," *RCA Corp v. Applied Digital Data Sys. Inc.*, 2212 USPQ 385, 388 (Fed. Cir. 1984). Inherent anticipation cannot be found unless the "prior art *necessarily* functions in accordance with limitations of a process or method claim" (*In re King*, 23 USPQ 136, 138 (Fed. Cir. 1986)). "Inherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). Here, Example 14, on which, the Examiner relies, refers merely to a "purified form of the 64 K antigen" (col. 25, line 54-55). The '937 patent does

not indicate that the 64 K antigen has been purified to such an extent as to give 99% pure lower molecular weight GAD.

If one were to attempt to obtain a "purified form of the 64 K antigen" from pancreatic islet cells, the Examiner has not show that one would necessarily obtain 99% purity. In fact, one would be most unlikely to do so for several reasons. One difficulty limiting purification was the small quantities of pancreatic islet cells available and the fact that of this small amount of material, that 64 kDa antigen was known to constitute less than 0.1% of total islet proteins (Baekkeskov et al., *Diabetes* 38, 1133-1141 (1989)). A second difficulty was the absence in the '937 patent of a simple and specific assay by which the yield of antigen could be assessed at each step in a purification procedure. A third difficulty was the need to achieve purification without impairing the 64 kDa antigen for subsequent use of the antigen in a pharmaceutical composition. In any event, regardless of the degree of difficulty of purifying the 64 kDa antigen from pancreatic cells, the Examiner has not met his burden of proving that a "purified form of the 64 K antigen" from pancreatic cells is necessarily at least 99% pure lower molecular weight GAD.

If one were to purify a form of the 64 kDa autoantigen from the CNS or from cells expressing recombinant GAD, one would not, based on the teaching of the patent, necessarily obtain lower molecular weight GAD rather than higher molecular weight GAD or a mixture thereof. The two forms naturally exist as a mixture in the CNS (see specification at p. 5, lines 26-28) and one would thus naturally purify a mixture of GAD unless taught to do otherwise. The '937 patent does not provide any such teaching. If one sought to purify GAD from cells expressing GAD recombinantly one would obtain whatever form of GAD was being expressed. The '937 patent does not provide any teaching to express the lower molecular weight form of GAD recombinantly. In fact, it provides the sequence of the higher molecular weight form (see Figs. 1A, B, and C)[1].

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[1] That Fig. 1 represents the sequence of higher molecular weight GAD can be determined as follows. The '937 patent references Kobayashi et al., *J. Neuroscience* 7, 2768-2772 (1987) as the source of the sequence (see col. 18, lines 59-64). GenBank entry P14748 corresponding to the cited Kobayashi paper characterizes the sequence described by Kobayashi as GAD67.

Therefore, regardless of whether one sought to purify the 64 kDa antigen from the pancreas, or obtain GAD from its natural source or by recombinant expression, one would not following the teaching of the '937 patent necessarily arrive at a pharmaceutical composition containing at least 99% w/w pure lower molecular weight GAD.

4. Alleged Obviousness of Claims 50-53, 66 and 67 Should be Determined by Interference; Claim 59 Would Not Have Been Obvious Over US 5,762,937

For purposes of this appeal, appellants do not dispute the substance of the rejection with respect to claims 50-53, 66 and 67. However, appellants do allege that they invented the above claims before the inventors of the '937 patent. Because the rejection is made at least in part over the claims of the '937 patent (final office action at paragraph 10), this issue can be resolved only by interference. Appellants have formally requested as interference with the '937 patent, as noted above.

Claims 59 would not have been obvious over the '937 patent for analogous reasons that claim 54 is not anticipated by the above patent. Claim 59 requires that the GAD used in therapeutic methods or compositions is human GAD65 at a purity of at least 99% w/w. As discussed in connection with claim 54, such a level of purity of lower molecular weight GAD is not inherent in the reference to a purified form of the 64 kDa antigen. It would not have been obvious to purify lower molecular weight GAD to 99% purity from pancreatic cells for the reasons discussed above in connection with claim 54. It would not have been obvious to purify lower molecular weight GAD from the CNS or cells recombinantly expressing GAD based on the teachings of the '937 patent also for the same reasons discussed for claim 54. That is, the '937 patent does not provide any teaching that there are two forms of GAD much less that one should purify the lower form from the higher form in the mixture that naturally occurs in the CNS. The '937 patent also does not provide any teaching to recombinantly express the lower molecular weight form as distinct from the higher molecular weight form for which it provides the sequence.

For these reasons, it is respectfully submitted that it would not have been obvious to prepare a composition comprising human lower molecular weight GAD of at least 99% purity with a pharmaceutical carrier as claimed.

5. Claims 35 and 54-57 Would Not Have Been Obvious Under 35 USC 103(a) over US 4,086,142 in view of US 4,736,020

The '142 patent is cited as teaching a composition in pharmaceutically acceptable carrier comprising GAD (citing to col. 14, lines 14-16). The Examiner acknowledges that the reference does not each that the composition is at least 99% w/w pure. The '020 patent is cited as teaching purity of a polypeptide to at least 99%. The Examiner takes the view that it would have been obvious to combine the teachings of the references in that purification of polypeptides to the desired purity was well-known in the art, and it would generally be preferable to use more pure reagents.

It is respectfully submitted that neither the feasibility of purifying proteins to 99% nor the general preference for use of pure reagents would have provided sufficient motivation to combine the teachings of the references. The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993). An "assertion that one of ordinary skill in the relevant art would have been able to arrive at applicant's invention because he had the necessary skills to carry out the requisite process steps" is an "inappropriate standard for obviousness." *Orthokinetics Inc. vs. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). Here, the '020 patent purified TNF to at least 99% purity because it was intended for a pharmaceutical use (see col. 2, lines 10-12). The '142 patent does not disclose a pharmaceutical use for GAD, but rather proposes to use GAD as a chemical reagent to remove serum glutamate from serum as part of an in vitro analysis. Whereas it is advantageous for a pharmaceutical agent to be purified to at least 99% purity to avoid possible side effects from contaminating materials, such a level of purity is not necessary in an in vitro reagent whose use involves no possibility of side effects. It is well known that increasing the degree of purity involves tradeoffs in terms of reduction in yield, and time and expense to effect the production. In the circumstances, it is submitted that the skilled artisan would not be impelled to perform additional steps to purify the GAD of the '142 patent to a level suitable for pharmaceutical use when no pharmaceutical use for GAD is disclosed by the '142 patent.

Moreover, the '142 patent does not disclose a composition suitable for parenteral use to a human as claimed. Claim 35 is directed to a composition comprising glutamic acid

decarboxylase in a pharmaceutically acceptable carrier for parenteral administration to a human patient. The recitation "for parenteral administration to a human patient" is not merely a statement of intended use but also an implied constraint on the nature of the composition. For example, Remington's Pharmaceutical Sciences (of record and cited at p. 21, line 4 of the specification) in connection with preparation of parenteral compositions states at p. 1546 that:

> An inherent requirement for parenteral preparations is they be of the very best quality and provide the maximum safety for the patient....Even the thought of using inferior techniques or ingredients in a manufacturing process must not be countenanced.

Thus, a composition for parenteral administration to a human must be *inter alia* sterile and substantially free of pyrogens and particulate matter (*id* at p. 1567). By contrast, a laboratory preparation of a protein is not typically sterile, and also usually contains impurities that would have been removed by sterilization and manufacture under GMP conditions.

Here, the preparation discussed by the '142 patent is disclosed as being "crude" and dissolved in a buffer of 20 mM acetate and pH 5.5 (col. 14, lines 14-16). This is a laboratory preparation suitable only for analytical use. The '142 patent does not disclose that the preparation was sterilized, free of pyrogens or particulate matter, or otherwise prepared in accordance with good manufacturing practices. In these circumstances, it would have been, at the very least, grossly irresponsible, and probably, illegal to administer parenterally the preparation of the '142 patent to a human patient. Accordingly, the '142 preparation cannot be considered to have been a composition for parenteral administration to a human patient.

Claims 54-57 are distinguished over the combination of cited references on additional grounds. The reference does not disclose lower molecular weight GAD, as recited in claim 54, recombinant GAD, as recited in claim 55, GAD synthesized on a peptide synthesizer as recited in claim 56, or GAD purified from the central nervous system, as recited in claim 57.

VIII. CONCLUSION

For the above reasons, appellants respectfully request that all rejections be reversed, and remanded for allowance of claims 54 and 59, and declaration of an interference between the present application and University of Florida, US 6,001,360 and US 5,762,937 for the remaining claims.

Respectfully submitted,

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IX. CLAIM APPENDIX

Claim 31 A method for inhibiting the development of insulin dependent diabetes mellitus, said method comprising administering to a patient a therapeutically effective dosage of glutamic acid decarboxylase (GAD).

Claim 35 A composition comprising glutamic acid decarboxylase, which is at least 99% w/w/ pure, in a pharmaceutically acceptable carrier for parenteral administration to a human patient.

Claim 50 The method of claim 31, wherein the GAD is recombinant GAD.

Claim 51 The method of claim 31, wherein the GAD is synthesized on a peptide synthesizer.

Claim 52 The method of claim 31, wherein the GAD is purified from the central nervous system tissue.

Claim 53 The method of claim 31, wherein the patient is a prediabetic patient having autoantibodies to GAD.

Claim 54 The composition of claim 35, wherein the GAD is lower molecular weight (GAD65).

Claim 55 The composition of claim 35, wherein the GAD is recombinant GAD.

Claim 56 The composition of claim 35, wherein the GAD is synthesized on a peptide synthesizer.

Claim 57 The composition of claim 35, wherein the GAD is purified from the central nervous system tissue.

Claim 59 The composition of claim 54, wherein the GAD65 is human GAD65.

Claim 62 A method of preventing or inhibiting the development of insulin dependent diabetes, wherein said method comprises administering to a patient at least 99% w/w pure GAD protein or a fragment thereof, which, when administered to the patient, prevents or inhibits the development of insulin dependent diabetes.

Claim 63 The method of claim 62, wherein the GAD protein or fragment thereof is a recombinant protein.

Claim 64 The method of claim 31, wherein the GAD is administered intravenously.

Claim 65 The method of claim 62, wherein the GAD or fragment is administered intravenously.

Claim 66 The method of claim 31, wherein the GAD is administered subcutaneously.

Claim 67 The method of claim 62, wherein the GAD is administered subcutaneously.

X. EVIDENCE APPENDIX

Baekkeskov declaration filed May 20, 2003, and resubmitted July 22, 2003, entered by office action of July 29, 2003.

Tisch *et al.*, *Nature* 366, 71-75 (1993), cited in Information Disclosure Statement submitted August 5, 1997, entered by office action of April 28, 1998.

Kaufman, *Nature* 366, 69-71 (1993), cited in Information Disclosure Statement submitted August 5, 1997, entered by office action of April 28, 1998.

Tian *et al.*, *Nature Medicine* 12, 1348 (1996), cited in appellants' communications of October 28, and October 30, 1998, entered by office action of January 22, 1999.

Peterson *et al.*, *Diabetes* 44, 1478 (1994), cited in appellants' communications of October 28 and October 30, 1998, entered by office action of January 22, 1999.

Harrison, *Molecular Medicine* 1, 722-727 (1994), cited and entered by office action of April 28, 1998.

(Benjamini & Leskowitz, *Immunology: A Short Course* (Liss, 1988) at p. 256), cited in communication submitted October 28, 1998, entered by office action of January 22, 1999.

Press Release attached to response of January 5, 2001, entered by office action of April 24, 2001.

Press Release filed July 22, 2003, resubmitted December 8, 2004, entered by advisory action of April 21, 2004.

XI. RELATED PROCEEDINGS APPENDIX

An interference is expected to be declared between USSN 08/452,053, the parent of the present US 5,645,998. However, the interference has not yet been declared and no Decision of the Board or a court exists.

PATENT
Docket No.: 2307AA-031220US
Client Ref. No.: 90-160-5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 8923
Steinunn Baekkeskov et al.	Examiner: Gerald R. Ewoldt
Application No.: 08/838,486	Technology Center/Art Unit: 1644
Filed: April 7, 1997	Petition of Denial of Entry of Exhibits and Declaration under 37 CFR 1.195.
For: IMPROVED METHODS FOR THE DIAGNOSIS AND TREATMENT OF DIABETES	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This paper requests review and reversal of the Examiner's decision refusing to enter new evidence submitted with the revised appeal brief filed August 13, 2004.

Statement of Facts

The present application provides evidence that glutamic acid decarboxylase is the major autoantigen in insulin dependent diabetes mellitus (IDDM, also known as type 1 diabetes). The present claims are directed to methods and compositions for treating IDDM using GAD to induce tolerance. Applicants had previously provided evidence regarding a clinical trial to test

the effect of GAD in a subset of diabetes patients termed LADA (late autoimmune diabetes in adults) (see submission of May 20, 2003, which was resubmitted July 22, 2003).

In the final office action, the Examiner took the position that the evidence regarding the clinical trial was not probative because the patients were not suffering from an autoimmune disease ("The best the Declarant can provide are preliminary results achieved in a related pathology of non-autoimmune origin (type II diabetes)," final office action of July 29, 2003 at p. 4, first paragraph). The Examiner also argued for the first time that alleged failure to establish tolerance in humans over the 13 years since the priority date of the application was evidence of nonenablement ("...some 13 years post-filing the establishment of tolerance in humans cannot be considered to be routine" (final office action at p. 4, first paragraph).

With an appeal brief filed April 29, 2004, applicants attempted to introduce a declaration of Dr. Baekkeskov and two exhibits providing evidence that the LADA patients on which the clinical trial were performed did have an autoimmune form of diabetes, contrary to the Examiner's position in the final office action. Applicants also attempted to introduce a review article, Findlay, Food and Drug Law Journal 54, 228 (1999), to show that an interval of 13 years between discovery of a drug and obtaining FDA approval was actually less than the average time required for approval of a drug.

In a communication mailed July 13, 2004, the Examiner refused to enter the new evidence on the basis that the final office action presented no new rejections or grounds for rejection.

In a response filed August 13, 2004, applicants submitted a revised appeal brief, and evidence together with a communication under 37 CFR 1.195 explaining why the new evidence should be entered under the appropriate standard. It is the evidence submitted with this communication for which review is requested by the present petition. This evidence consists of a declaration by co-inventor Dr. Baekkeskov,[1] exhibits to the declaration from DiabetesMonitor.Com and a Diamyd Press Release, and a review article, Findlay, Food and Drug Law Journal 54, 228 (1999).

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[1] A previously submitted declaration of Dr. Baekkeskov has been entered and is not at issue in this petition.

In a communication mailed October 27, 2004, the Examiner again refused to enter the new evidence, this time on the basis that it had not been submitted in a separate paper from the appeal brief.

In a response dated November 11, 2004, applicants pointed out that the request to enter new evidence had been submitted in a separate paper. Applicants also reiterated the grounds on which the evidence should be admitted under the appropriate standard.

On July 8, 2005, September 27, 2005 and March 1, 2006, applicants submitted three separate request for the status of the Examiner's response to their communication of November 11, 2004.

On June 1, 2006, the Examiner issued a communication again refusing to enter the new evidence, repeating his remarks of July 13, 2004 that no new rejection or ground of rejection had been made. The Examiner added that the asserted new allegations and arguments were in response to the inventor's declaration of May 23, 2004.[2]

The present petition follows.

The Standard of Review

As of the date of submitting the new evidence, August 13, 2004, the standard for determining admission of such evidence was provided by 37 CFR 1.195. It is recognized that the standard has now changed, and has become more restrictive (37 CFR 41.33). However, the new standard was not in effect at the time the evidence was filed (August 13, 2004). Accordingly, it is respectfully submitted that the admissibility is determined by 37 CFR 1.195, which reads as follows:

> Affidavits, declarations, or exhibits submitted after the case has been appealed will not be admitted without a showing of good and sufficient reason why they were not presented earlier.

Analysis

[2] This declaration was actually filed May 20, 2003 and resubmitted July 22, 2003.

The Baekkeskov declaration and its exhibits and the Findlay reference address new points of argument by the Examiner in the final office action. The exhibits and declarations could not have been presented earlier because the arguments they address were not presented before the final office action by the Examiner.

The Baekkeskov declaration and the associated exhibits from DiabetesMonitor.Com and the Diamyd Press Release cited in the Baekkeskov declaration were submitted to rebut the Examiner's allegation in the final office action that the phase II clinical trial described in the previous Baekkeskov declaration was conducted on patients suffering from a "related pathology of non-autoimmune origin" (final office action at p. 4, first paragraph). The Examiner had not made this allegation or anything like it previously in prosecution. The second Baekkeskov declaration and the associated references show that in fact the patients in the clinical trial suffer from Late Autoimmune Diabetes in Adults (LADA), a type of diabetes characterized by autoimmune destruction of the pancreas and generally recognized as being a form of type I diabetes. Thus, the second Baekkeskov declaration and associated references address new argument in the final office action and could not have been submitted earlier.

Findlay, Food and Drug Law Journal 54, 228 (1999) was submitted to rebut a further new argument of the Examiner in the final office action in which the Examiner attempted to buttress his case of nonenablement with the assertion that "even now, some 13 years post-filing, the establishment of tolerance in humans cannot be considered to be routine" (final office action at p. 4, first paragraph). In response, it is relevant to point out that a delay of 13 years between filing a patent application and clinical success is nothing unusual. As noted by Finlay, the average time between drug discovery and marketing is 14.7 years. Once again, the Examiner's argument based on the interval between filing of the application and establishing tolerance in humans was newly made in the final office action, and could not have been addressed earlier.

The Examiner does not appear to dispute that new arguments were made in the final office action in that he acknowledges that these arguments were in response to a declaration filed May 20, 2003 (i.e., shortly before the final office action). However, the Examiner has

consistently taken the position (Notification of Non-Compliance of July 13, 2004 and June 1, 2006) that he can refuse entry of the requested evidence because "no new rejections nor grounds for rejection were made by the Examiner." In applicant's submission, the Examiner's position does not apply the standard of 37 CFR 1.195 (or for that matter of 37 CFR 41.33). Regardless whether the Examiner's new arguments were responsive to new evidence by applicant or other reason, the fact remains that the arguments were new and could not have reasonably been addressed by applicants before the new arguments were made. Thus, under 37 CFR 1.195, which was in effect on August 13, 2004 when the evidence was offered, the evidence should have been admitted.

For these reasons, applicants respectfully submit that the new arguments in the final office action provide good and sufficient reason why the Baekkeskov declaration, its exhibits and the Findlay reference were not presented earlier. Accordingly, entry under 37 CFR 1.195 is respectfully requested.

Applicants understand that the present petition does not toll the period for submission of a revised brief. Accordingly, a revised brief has been filed without the requested evidence. If the petition is granted, applicants request the new evidence be introduced in a supplemental submission or the reply brief.

Please charge the fee of $130 for this petition to deposit account 20-1430. Please charge any additional amount or credit any overpayment to the same account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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